CANCER RESEARCH

How TRAIL Kills Cancer Cells, But Not Normal Cells

Even when battered by heavy-duty chemotherapy and radiation, cancer cells all too often don't give up. In about half of all tumors, this tenacity stems in part from mutations in the cells' *p53* tumor suppressor gene, which render it incapable of performing one of its key functions: activating an internal suicide program after the DNA has been damaged by drugs or x-rays.

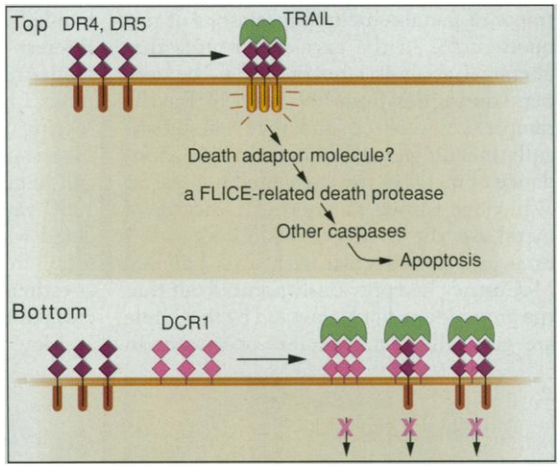
About a year and a half ago, however, researchers made a discovery that raised hopes that they might still get such mutated cancer cells to kill themselves: Tumor cells are far more susceptible than healthy ones to another suicide signal, a protein called TRAIL, which acts independently of *p53*. At the time, though, this hypersensitivity to TRAIL was a mystery. Now three groups, two of them writing in this issue, may have solved the puzzle by showing that normal cells, but not cancerous ones, have a "decoy" protein that can throw TRAIL off the scent.

On pages 815 and 818, Avi Ashkenazi's group at the biotech firm Genentech Inc., in South San Francisco, and Vishva Dixit of the University of Michigan Medical School in Ann Arbor and his colleagues report the discovery of two new receptor proteins for TRAIL. One transmits TRAIL's message into the cell interior. But the other, although it can bind the death-inducing protein, is incapable of transmitting its signals. A team at Immunex Corp. in Seattle, led by Ray Goodwin and Craig Smith, has come up with similar results that are in press in the *Journal of Experimental Medicine*. The researchers find this decoy receptor, called either DcR1 (for decoy receptor 1) or TRID (TRAIL receptor without an intracellular domain), in many types of normal human tissues, but not in most cancer cell lines.

Researchers have long known that viruses help protect themselves against immune attack by cranking out dummy receptors for the molecules that recruit dangerous immune cells. But the TRAIL finding is the first evidence that the body's own cell-bound proteins can serve as decoys against death-inducing proteins. "What is pretty neat is this shows that the body can do it, too," says Craig Thompson, an apoptosis researcher at the University of Chicago.

The decoy protein's function is unknown, as is the function of TRAIL itself. But Thompson and others think that the new findings could aid efforts to exploit the TRAIL pathway to kill cancer cells selectively. "This work suggests there might be specific ways to intervene in the survival regulation of cells," he says.

Researchers studying programmed cell death, or apoptosis, have been trying to solve the mystery of why cancer cells are so susceptible to TRAIL almost from the time of its discovery in 1995 by Goodwin's team at Immunex and by Ashkenazi and his colleagues. At first, they reasoned that tumor cells are preferentially killed by TRAIL because the cells exclusively express an unknown TRAIL receptor that normal cells lack.



SOURCE: V. DIXIT ILLUSTRATION: K. SUTLIFF

Decoying death. The decoy receptor DcR1 can't trigger apoptosis on its own and may also interfere with signaling by TRAIL receptors DR4 and DR5.

But when Dixit and his colleagues at Michigan and Human Genome Sciences in Rockville, Maryland, identified the first TRAIL receptor, a protein called DR4 (for death receptor 4), in April of this year, the discovery created more questions than it answered (*Science*, 4 April, p. 111). Both normal and tumor cells appeared to produce similar amounts of DR4. That sent researchers to the DNA databases looking for sequences indicating other TRAIL receptors.

Those sequences had to fit one main criterion: They had to resemble a DNA segment that encodes the so-called "death domain," a stretch of 60 to 80 amino acids found in receptors for other apoptosis-inducing molecules that is essential for their activity. Working independently with two separate databases, Ashkenazi's and Dixit's groups both pulled out a TRAIL receptor sequence, called DR5. Meanwhile, the Immunex team purified the DR5 protein from membrane extracts of TRAIL-sensitive cells. But to everyone's dismay, both normal and cancer cells expressed DR5 messenger RNA, implying that both kinds of cells produced this receptor as well.

The researchers made another visit to the databases. Instead of searching for the death domain, they simply looked for sequences that resemble the putative TRAIL-binding region of DR4. Almost immediately, the investigators pulled out another gene that turned out to encode the so-called decoy receptor.

This sequence encodes a protein that contains the external TRAIL-binding region, as well as a stretch of amino acids that anchors the receptor to cell membranes. But the new receptor, DcR1, lacks the intracellular segment needed to spark the cell-death pathway. Most importantly, the receptor is expressed almost exclusively by normal cells.

Further evidence that DcR1 acts a decoy came when the researchers introduced the gene into tumor cell lines normally killed by TRAIL and found that it dramatically reduced the cells' susceptibility to apoptosis. "It appears that we found a decoy receptor that is highly expressed in normal cells and protects them from the death pathway," concludes Dixit. However, he and others are at a loss to explain why normal cells carry such a receptor, while tumor cells do not. "It doesn't make sense," Thompson says. "Tumor cells have evolved to not want to die, so this is really puzzling."

That isn't stopping researchers from pondering how the discovery might be parlayed into novel cancer therapies. Researchers have been looking for cell suicide signals that don't involve *p53* that might be wielded against cancer cells. One such signal, the apoptosis-inducing protein known as tumor necrosis factor (TNF), triggers severe inflammatory reactions, but TRAIL seems to lack this drawback. "This may be the long-sought-after means to obtain *p53*-independent cell death using a molecule that doesn't possess the toxicity of previously tried agents like TNF," says Dixit.

Researchers at Genentech and Immunex have already begun testing TRAIL in rodents with cancer to see whether it, either alone or in combination with traditional therapies, might thwart tumor growth. So far there have been no signs of toxicity. But animal studies have just begun, and it's too early to tell whether the novel treatment will work or exactly how the new decoy findings will help.

Indeed, researchers caution that a great deal needs to be learned about TRAIL. "We don't have a clue yet of what TRAIL does biologically," says Thompson. Still, he adds, "just the sheer complexity of it all says that this is really important. After all, death is an important decision that a cell cannot make twice."

–Trisha Gura